Remarks

Claims 1-9 , 14, 15, and 37 are pending in the subject application. Applicants gratefully acknowledge the Examiner's withdrawal of the objections to the claims and certain of the previous rejections under 35 USC §102. By this Amendment, Applicants have amended claim 1 and canceled claims 14, 15, and 37. Support for the amendments can be found throughout the subject specification. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-9 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 1-9, 14, 15, and 37 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. The Examiner asserts that the subject specification does not enable treatment of any vascular disorder other than intimal hyperplasia in any species other than a rabbit using a DNA expression vector encoding a VEGF receptor agonist which is not an agonist for either an Flt-1 or a FLK-1/KDR receptor. As noted above, claims 14, 15, and 37 have been canceled, thereby rendering this rejection of these claims moot.

Applicants respectfully assert that the claims are enabled by the subject specification and that a nucleic acid encoding an agonist of any VEGF receptor can be used in the claimed method. However, in a sincere effort to expedite prosecution of the subject application to completion, Applicants have amended claim 1 to recite that the nucleic acid encodes an agonist of a Flt-1 or Flk-1/KDR receptor.

In regard to the Examiner's comments that the claims do not limit the mode of delivery of nucleic acids, Applicants respectfully note that claim 1 specifies that the method comprises "periadventitial administration to said blood vessel" being treated. In addition, claim 1 has been amended to recite that administration of the agent occurs at the site of injury. This is in accordance with what the Examiner has indicated is enabled as set forth at page 7 of the instant Office Action. In addition, attached with this Amendment is the signed Declaration of John Francis Martin, M.D. Under 37 CFR 1.132 which shows that nucleic acid encoding a VEGF receptor agonist was successfully delivered and expressed in targeted blood vessel cells. Applicants respectfully request that Dr. Martin's Declaration be considered and made of record in the subject application. In the attached Declaration, Dr. Martin summarizes Applicants' pre-clinical data for the use of VEGF in the

treatment of intimal hyperplasia. As Applicants noted in the Amendment dated May 16, 2002, this data was recently presented to the Recombinant Gene Advisory Committee of the National Institutes of Health, and the Food & Drug Administration, as part of the process for obtaining approval to perform clinical trials. Accordingly, Applicants respectfully assert that the subject specification enables the claimed nucleic acid-mediated treatment methods.

In regard to the Examiner's comments that the rabbit animal model is not predictive for humans, Applicants respectfully assert that the subject specification enables the claimed method for the treatment of mammals, including pigs and humans. It is well established in patent law that studies in humans are not required for claims where there is an animal model that is accepted in the art. Applicants respectfully assert that for studies directed to treatment of blood vessels in mammals, the rabbit animal model is well accepted in the art and has been used extensively in studies reported in the scientific literature. Submitted with this Amendment are references by Strauss *et al.* (*Int. J. Radiation Oncology Biol. Phys.*, 2002, Vol. 54, No. 2) and Farb *et al.* (*Circulation*, 2001, Vol. 103) which show that the rabbit is a suitable animal model and is used in studies for testing suitability of procedures in humans. Applicants note that the authors of the Farb *et al.* reference, at page 1917, column 2, indicate that "the results of the present study suggest the rabbit iliac artery may be the superior animal model to study responses likely to be seen in humans." (emphasis added) If the rabbit model was not a valid model for procedures in humans, Applicants respectfully assert that clinical researchers would not use it for their studies and it is unlikely that studies using rabbits would be published in the scientific literature. The fact that the rabbit model continues to be used in published scientific studies is evidence that the rabbit is a valid model for other mammals, including humans.

Porcine and canine models are also used in the art. As noted in Dr. Martin's Declaration, Applicants have also conducted the claimed method on pigs with positive results. Applicants maintain that the information relating to the pig study described in Dr. Martin's Declaration is particularly relevant, as it shows that VEGF can have an effect across species. The Food & Drug Administration suggested the use of pig data for purposes of predicting suitability for human clinical trials.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-9, 14, 15, and 37 are rejected under 35 USC §112, second paragraph, as indefinite. Specifically, the Examiner states that the claims do not recite a step in which is treatment effected and do not require any specific outcome as a result of the method steps. Applicants respectfully assert that the claims as filed are definite. However, as noted above, claims 14, 15, and 37 have been canceled, thereby rendering this rejection of these claims moot. In addition, claim 1 has been amended to recite that intimal hyperplasia of the blood vessel is prevented or reduced as a consequence of the method. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 14, 15, and 37 are rejected under 35 USC §102(e) as anticipated by Isner (either of U.S. Patent Nos. 6,121,246 or 6,258,787) and under 35 USC §102(a) as anticipated by Isner *et al.* (1996) or Takeshita *et al.* (1996). Applicants respectfully assert that the patents or references do not anticipate the claimed invention. However, by this Amendment, Applicants have canceled claims 14, 15, and 37. Thus, the §102 rejections are moot. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §§102(e) and 102(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRP/sl
Attachments: Marked-Up Version of Amended Claim; Declaration of Dr. John Francis Martin Under 37 CFR 1.132 (signed); copy Strauss *et al.* reference; copy of Farb *et al.* reference.

Marked-Up Version of Amended Claim

Claim 1 (thrice amended):

1. A method for the treatment or prevention of intimal hyperplasia of a blood vessel of a person or animal, where the endothelium of said blood vessel is intact, wherein said method comprises periadventitial administration to a site of injury of said blood vessel of said person or animal of an amount of an agent that is effective to treat or prevent intimal hyperplasia of said blood vessel, wherein said agent comprises a nucleic acid that encodes an agonist of a Flt-1 or a Flk-1/KDR receptor to which VEGF binds and expressing said agonist encoded by said nucleic acid in the cells of said blood vessel, whereby intimal hyperplasia of the blood vessel is prevented or reduced.